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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/533,290	02/07/2006	Thor Las Holtet	08-349-WO-US	6045

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EXAMINER	
MERTZ, PREMA MARIA	

ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,290	HOLTET ET AL.	
	Examiner	Art Unit	
	Prema M. Mertz	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,18-23,30 and 35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 18-23, 30, 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/12/09 has been entered.

2. Claims 2-17, 24-39, 31-34, have been cancelled previously.

Amended claims 1, 18-22, 35 (6/12/09) and previous claims 23 and 30 are pending and under consideration by the Examiner.

3. Receipt of applicant's arguments and amendments filed on 6/12/2009 is acknowledged.

4. The following previous rejections and objections are withdrawn in light of applicants amendments filed on 6/12/2009:

(i) the rejection of claims 35 under 35 U.S.C. 112, second paragraph.

5. Applicant's arguments filed on 6/12/09 have been fully considered and were persuasive in part. The issues remaining and new issues are stated below.

6. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim rejections-35 USC § 112, first paragraph, written description

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7a. Claims 1, 18-23, 30, 35, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

This rejection is maintained for reasons of record set forth at pages 2-6 of the previous Office action (8/22/2008) and pages 2-10 of the previous Office action (2/12/2009).

Applicants argue that with respect to the portion of each monomer that specifically binds a trimeric cytokine, the specification states that the monomers of the disclosed trimeric polypeptides comprise a specific binding member capable of binding a trimeric cytokine (specification, page 6), the specification defines a specific binding member as "a member of a pair of molecules which have binding specificity for one another" (specification, page 8), and defines trimeric cytokines as being "small proteins and fragments thereof, which are produced and secreted by a cell, and which elicit a specific response in a cell which has a receptor for that cytokine, e.g. by affecting the growth, division and/or function of the cell" (specification, page 6), the specification also lists a number of examples of trimeric cytokines, **including** macrophage migration inhibitory factor (MIF) and cytokines within the tumor necrosis factor ligand super family (TNFLSF) (specification, page 7), which includes at least seventeen recognized ligands

(i.e., lymphotoxin alpha (LTA), tumor necrosis factor (TNF), lymphotoxin beta (LTB), OX-40L, CD40L, FasL, CD27L, CD30L, 4-1BB-L, TRAIL, RANKL, TWEAK, APRIL, BAFF, LIGHT, VEGI, and GITRL; specification, page 8; *see also* Table 1 on page 7 of specification) that share a conserved trimeric C-terminal domain known as the "TNF homology domain" (THD) (specification, page 7), and the specification lists a number of examples of specific binding members that are capable of binding a trimeric cytokine, **including** receptors within the tumor necrosis factor superfamily ***(e.g.,*** TNFRSF1A, TNFRSF1B, LTBR, TNFRSF4, TNFRSF5, TNFRSF6, TNFRSF6B, TNFRSF7, TNFRSFS, TNFRSF9, TNFRSF10A, TNFRSF 10B, TNFRSF 10C, TNFRSF 10D, TNFRSF 11 A, TNFRSF 11 B, TNFRSF12, TNFRSF 12L, TNFRSF13B, TNFRSF13C, TNFRSF14, NGFR, TNFRSF17, TNFRSF18, TNFRSF19, TNFRSF 19L, TNFRSF21, TNFRSF22, and TNFRSF23; specification, page 10; *see also* Table 2 on pages 9-10. Furthermore, Applicants argue that the specification discloses that sequences having the scaffold structure of C-type lectin-like domains (CTLD), such as the human tetranectin-based CTLD, **may be** capable of binding trimeric cytokines such as TNF (specification, page 12) and Applicants contend, therefore, that in view of the disclosure in the specification, one of ordinary skill in the art would readily recognize the types of molecules that are encompassed by the phrase "trimeric cytokine," the types of the molecules that would be capable of specifically binding a trimeric cytokine, and thus, could readily envision the structure of the portion of the claimed trimeric polypeptide that specifically binds a trimeric cytokine. However, contrary to Applicants arguments, the disclosure in the specification recites the terms "including" which is exemplary and "may be" which is a conditional. Except for a trimeric polypeptide comprising three monomers, wherein each monomer comprises the amino acid

sequence set forth in SEQ ID NO:106 or SEQ ID NO:107 or SEQ ID NO:108, and each monomer comprises a specific cytokine binding domain and a tetranectin trimerising domain wherein the tetranectin trimerising domain comprises the amino acid sequence of SEQ ID NO:81, Applicants have failed to provide a written description for any other trimeric polypeptide. Applicants are reminded that "Argument of counsel cannot take the place of evidence lacking in the record" (*In re Scarbrough*, 182 USPQ 298, 302 (CCPA 1974)).

It is suggested that Applicants amend the claims to recite the embodiments for which there is written description the instant specification.

Claim Rejections - 35 U.S.C. § 112, first paragraph, scope of enablement

7b. Claims 1, 18-23, 30, 35, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a trimeric polypeptide comprising three monomers, wherein each monomer comprises the amino acid sequence set forth in SEQ ID NO:106 or SEQ ID NO:107 or SEQ ID NO:108, and each monomer comprises a specific cytokine binding domain and a tetranectin trimerising domain wherein the tetranectin trimerising domain comprises the amino acid sequence of SEQ ID NO:81, does not reasonably provide enablement for as recited in claims 1, 18 and 19. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection is maintained for reasons of record set forth at pages 7-9 of the previous Office action (8/22/2008) and pages 10-13 of the previous Office action (2/12/2009).

Applicants argue that the specification provides enablement for the genus of trimeric polypeptides recited in claims 1, 18, and 19, and the specification contains substantial teachings about the portion of the claimed trimeric polypeptide that is a specific binding member capable of binding a trimeric cytokine, and further, states that the trimerising domain that is derived from tetranectin of the claimed trimeric polypeptides comprises a tetranectin trimerising structural element (also called TTSE), which is described in detail in International Publication No. WO 98/56906 (the '906 publication) and therefore, one of ordinary skill in the art would therefore readily recognize how to make and use the claimed trimeric polypeptides of the instant invention. However, contrary to Applicants arguments, the issue here is the breadth of the claims in light of the predictability of the art as determined by the number of working examples, the skill level of the artisan and the guidance presented in the instant specification and the prior art of record. This position is consistent with the decisions in In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) and Amgen Inc. V. Chugai Pharmaceuticals Co. Ltd., 13 USPQ2d, 1737 (1990), and In re Wands, 8USPQ2d, 1400 (CAFC 1988) (which has been cited by Applicants. If Applicants will kindly review page 1404 of In re Wands, they will find that the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims. Applicants arguments that the standard is that of obtaining a subject trimeric polypeptide that has a portion which is a specific binding member capable of

binding a trimeric cytokine, and testing to see if it retains the desired biological activity is a position that has been routinely dismissed by the courts, as shown by the decisions cited above.

Further, In re Wands determined that the repetition of work which was disclosed in a patent application as producing a composition containing an antibody, which is a naturally-occurring compound, did not constitute undue experimentation even if the antibody produced thereby was not identical to those that were disclosed in that application. The instant claims are not limited to naturally-occurring compounds and the instant specification does not provide a description of a repeatable process of producing the claimed trimeric polypeptide whose tetranectin trimerising domain amino acid sequence deviates from the disclosed sequence by as much as 17%. To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the determination of those amino acid residues which are required for functional and structural integrity of those proteins. It is this additional characterization of the disclosed protein that is required in order to obtain the functional and structural data needed to permit one to produce a trimeric protein which meets both the structural and functional requirements of the instant claims that constitutes undue experimentation.

Furthermore, Applicant is encouraged to review the discussion of 35 U.S.C. § 112, first paragraph, in a recent CAFC decision, Genentech, Inc. v. Novo. Nordisk, 42 USPQ2d, 100 (CAFC 1997), in which the decisions in In re Fisher, Amgen Inc. V. Chugai Pharmaceuticals Co. Ltd., and In re Wands were considered as the controlling precedents in determining enablement issues where protein and recombinant DNA issues are concerned. These decisions have been

relied upon in the instant rejection and by the Court because they show that the judicial interpretation of the first paragraph of 35 U.S.C. § 112 requires that the breadth of claims must be based upon the predictability of the claimed subject matter and not on some standard of trial and error. To argue that one can make material embodiments of the invention and then test for those that work in the manner disclosed or that the instant claims only encompass the working embodiments is judicially unsound. Unless one has a reasonable expectation that any one material embodiment of the claimed invention would be more likely than not to function in the manner disclosed or the instant specification provides sufficient guidance to permit one to identify those embodiments which are more likely to work than not, without actually making and testing them, then the instant application does not support the breadth of the claims. In the instant case it is highly improbable that a trimeric protein having a tetranectin trimerising domain with amino acid sequence identity of 87% or 92% identity to that disclosed in SEQ ID NO:81 will more likely than not perform in the manner disclosed and the instant specification does not provide the guidance needed to predictably alter the sequence with any reasonable expectation that the resulting protein will have the desirable activity.

Applicants argue that the specification states that the monomers of the disclosed trimeric polypeptides comprise a specific binding member capable of binding a trimeric cytokine (specification, page 6), and defines the terms "specific binding member" and "trimeric cytokine" (specification, pages 6 and 8), the specification also lists a number of examples of trimeric cytokines, **including** macrophage migration inhibitory factor (MIF) and cytokines within the tumor necrosis factor ligand super family (TNFLSF) (specification, page 7), which **includes** at least seventeen recognized ligands ***(i.e.,*** lymphotoxin alpha (LTA), tumor necrosis factor (TNF),

lymphotoxin beta (LTB), OX-40L, CD40L, FasL, CD27L, CD30L, 4-1BB-L, TRAIL, RANKL, TWEAK, APRIL, BAFF, LIGHT, VEGI, and GITRL; specification, page 8; *see also* Table 1 on page 7 of specification) that share a conserved trimeric C-terminal domain known as the "TNF homology domain" (THD) (specification, page 7), the specification lists a number of examples of specific binding members that are capable of binding a trimeric cytokine, **including** receptors within the tumor necrosis factor superfamily *(e.g.,* TNFRSF1A, TNFRSF1B, LTBR, TNFRSF4, TNFRSF5, TNFRSF6, TNFRSF6B, TNFRSF7, TNFRSF8, TNFRSF9, TNFRSF10A, TNFRSF 10B, TNFRSF 10C, TNFRSF 10D, TNFRSF 11 A, TNFRSF 11 B, TNFRSF 12, TNFRSF 12L, TNFRSF13B, TNFRSF13C, TNFRSF14, NGFR, TNFRSF17, TNFRSF18, TNFRSF19, TNFRSF 19L, TNFRSF21, TNFRSF22, and TNFRSF23; specification, page 10; *see also* Table 2 on pages 9-10 and the specification discloses that sequences having the scaffold structure of C- type lectin-like domains (CTLD), such as the human tetranectin-based CTLD, **may be** capable of binding trimeric cytokines such as TNF (specification, page 12). Applicants argue that it is predictable that the trimeric polypeptides of the claimed invention can be constructed using the teachings of the specification and knowledge in the art, it is predictable that if each monomer of the claimed trimeric polypeptides contains a tetranectin trimerising structural element, as required by the pending claims, the monomers constituting the trimeric polypeptide will trimerize, thus generating a trimeric polypeptide and it is predictable that if each monomer contains a sequence that specifically binds a trimeric cytokine (such as the sequences disclosed in the specification), the trimeric polypeptide will bind a trimeric cytokine.

However, contrary to Applicants arguments, the disclosure in the specification recites the terms "including" which is exemplary and "may be" which is a conditional. Furthermore,

contrary to Applicants arguments, from the teachings of the instant specification, one of skill in the art would not be able to generate a monomer containing a modified tetranectin trimerising domain that would lead to trimerisation of the monomers and yield a trimeric polypeptide because the monomers recited in the specification are exemplary and except for a trimeric polypeptide comprising three monomers, wherein each monomer comprises the amino acid sequence set forth in SEQ ID NO:106 or SEQ ID NO:107 or SEQ ID NO:108, and each monomer comprises a specific cytokine binding domain and a tetranectin trimerising domain wherein the tetranectin trimerising domain comprises the amino acid sequence of SEQ ID NO:81, Applicants have failed to provide enablement for any other trimeric polypeptide. Applicants are reminded that "Argument of counsel cannot take the place of evidence lacking in the record" (*In re Scarbrough*, 182 USPQ 298, 302 (CCPA 1974)). It is suggested that Applicants amend the claims to recite the embodiments enabled by the instant specification.

Claim rejections-Double Patenting

Non-statutory double patenting rejection (obviousness-type)

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8a. Claims 1, 18-20, 30, are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 56-68 of copending Application No. 11/452,434 ('434). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 56-64, 80-81of copending Application No. 11/452,434 (having one common inventor with the instant application), claims a trimeric polypeptide complex comprising three monomer polypeptides, wherein (i) each of said monomer polypeptides comprises a tetranectin trimerising structural element (TTSE), said TTSE being a polypeptide having at least 68% amino acid sequence identity with the consensus sequence shown in SEQ ID NO:40 and (ii) at least one of said monomer polypeptides is covalently linked to at least one heterologous moiety, where said at least one heterologous moiety is different from any of the fusion proteins CIIH6FXTN123, H6FXTN123, H6FXTN12, H6FCTN23, the sequences of which are shown in SEQ ID NOs:24-27, and said complex remains as a trimer at a temperature of at least 60°C.

This rejection is maintained for reasons of record set forth at pages 9-11 of the previous Office action (8/22/2008) and pages 14-16 of the previous Office action (2/12/2009).

Applicants argue that they acknowledge the provisional rejection under the doctrine of obviousness-type double patenting, and elect to address this ground of rejection upon notification that this rejection has been made non-provisional, all other conditions for patentability have been met, and the instant claims are otherwise in condition for allowance. However, contrary to Applicants arguments, the instant claims will never be allowable unless a terminal disclaimer is filed to obviate the provisional nonstatutory obviousness-type double patenting rejection.

Conclusion

No claim is allowed.

Claims 1, 18-23, 30, 35, are rejected.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Prema Mertz whose telephone number is (571) 272-0876. The examiner can normally be reached on Monday-Friday from 7:00AM to 3:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on (571) 272-0835.

Official papers filed by fax should be directed to (571) 273-8300. Faxed draft or informal communications with the examiner should be directed to (571) 273-0876.

Information regarding the status of an application may be obtained from the Patent application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Prema Mertz/
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Primary Examiner
Art Unit 1646